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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

SERIAL NO.:	**08/160,965**	§	**DOCKET: P00965US0**
FILING DATE:	**12/02/93**	§	
APPLICANT:	**Musser et al.**	§	**EXAMINER: Ja-Na Hines**
TITLE:	**Vaccines Containing Cysteine Protease and Methods to Protect Against Group A Streptococci**	§	**ART UNIT: 1641**

OK to Enter
8/7/02

DECLARATION

Dear Sir:

The undersigned, James M. Musser, M.D., Ph.D., hereby declares and states that:

1. I am a co-inventor of subject matter claimed in the above-referenced patent application.

2. I have read the above-referenced application, and I have read the pertinent Office Action.

3. My current position is Chief, Laboratory of Human Bacterial Pathogenesis, Rocky Mountain Laboratories, National Institutes of Allergy and Infectious Diseases. I have been involved in vaccine research for over 10 years.

4. I have been asked to indicate that the two Kapur et al. references are my work and also to establish a long felt need for the development of a vaccine against Group A Streptococcus.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231 on JUNE 2, 2000
Shannon E. O'Brien
SEOBrien
Signature
6.2.2000
Date

5. I assert that the material contained in the papers Kapur et al., *Microbial Pathogenesis* 15:327-346, 1993 and Kapur et al., *Proc. Natl. Acad. Sci. USA*, 90:7676-7680, 1993 was material invented by myself and the co-inventor, Kapur; we were the sole inventors. The other authors on the papers were merely hands working under our direction.

6. I, James M. Musser, assert that claims 1-17, as made by James M. Musser and Vivek Kapur, were conceived and published in the Kapur et al. papers.

7. The sequence of amino acids that was published by Tai et al. contains several differences compared to the sequence of speB of the present invention. The most obvious difference between the protein structure of the present invention and the one published by Tai is the omission of 34 amino acids residues occurring between serine 84 and isoleucine 117. These differences have been determined to be to due protein sequencing artifacts. Thus, this published amino acid sequence is not complete.

8. The speB nucleotide sequence of the present invention resembles, but is distinct from the one described by Hauser and Schilevert. The specific sequence published by Hauser and Schilevert never demonstrated protelytic activity. The lack of protease activity was a consequence of the difference in amino acid sequence around the cysteine residue near the active site. We were able to characterize and establish protelytic activity in the present invention. Thus, the sequence of the present invention is functional, unlike the one published by Hauser and Schilevert.

9. The protein isolated by Gerlach et al. was estimated to be 30kD. The protein we have isolated was 40,314kD that can be transformed into an enzymatically active protease of 27,588kD by reduction and autocatalytic conversion.

10. It is my belief, as one skilled in the art, that the teachings in our specification enable one of skill to use the streptococccal cysteine protease as a vaccine. Our specification teaches that the streptococcal cysteine protease is an effective vaccine against streptococcal infections in humans, and that the vaccine should be administered in an amount sufficient to confer immunity

to Group A Streptococcal infection (p.7 lines 23-25). The skilled artisan can determine the appropriate dosage amount and inoculation regime by following well-established guidelines for peptide vaccines. In this case, the skilled artisan also has the benefit of past experience using a different streptococcal peptide, the M protein, as a human vaccine. For example, Beachey et al., used three doses of 200 μg protein administered subcutaneously every two weeks, followed by a fourth 200 μg dose 3-4 months after the first dose. Beachey et al. noted that these doses are "well-tolerated" and "within conventionally acceptable limits for vaccines in common use" (pp. 872-873, bridging sentence).

11. Similarly, our specification, coupled with conventional guidelines and experience using the streptococcal M protein as a vaccine, provide the skilled artisan with knowledge as to an appropriate vaccine formulation. Our specification teaches that the active ingredient in the vaccine formulation is the streptococcal cysteine protease (p. 7, lines 1-8). It is within conventional knowledge that peptide vaccines are normally administered in conjunction with and adjuvant. Experience using the streptococcal M protein as a vaccine provides relevant examples of suitable adjuvants. For example, Beachey et al., published a protocol for vaccinating humans using the streptococcal M protein. Beachey et al. used aluminum hydroxide gel as the adjuvant in their protocol because "aluminum-hydroxide gels have been well-tolerated in man and have shown to serve as good adjuvants for the stimulation of the immune responses to other vaccine antigens" (p. 866, second paragraph). Thus, one of skill would expect that aluminum hydroxide would be an effective adjuvant for the cysteine protease.

12. Furthermore, I believe that there is a long-felt need for the identification of an efficient streptococcus vaccine. In a 1999 article published in JAMA (Vol. 281, pgs. 1973-1977), Group A streptococcus (referred to as Group A strep) is the cause of "strep throat", and it can also cause severe invasive diseases such as toxic shock syndrome, acute rheumatic fever, and others. The search for a vaccine for Group A streptococcus began in 1906 and was banned by federal law for several years after 1979, following a vaccine trial that was associated with significantly more acute rheumatic fever among vaccinated subjects. However, there still has not been an effective vaccine developed for Group A Streptococcus. Thus, this would indicate that there is a long-felt need for a vaccine that would be beneficial to humans.

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13. I assert that until the present invention, no one in the field of *Steptococcus pyogenes* considered using the cysteine protease as a potential vaccine. The efforts were focused on the M protein as reported by Kehoe, (Vaccine 797-806, 1991). Thus, our use of cysteine protease as a vaccine against Group A Streptococcus is the first.

DECLARATION

I declare that all statements made here of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 1 JUNE 00

James M. Musser

James M. Musser, M.D., Ph.D.